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Lipophilic semisolid emulsion systems: viscoelastic behaviour and prediction of physical stability by neural network modelling

Mirjana Gašperlin [a], Livija Tušar [b], Marjan Tušar [c], Julijana Kristl [a], Jelka Šmid-Korbar [a,*]

[a] *Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia*
[b] *Krivec 3, 1126 Ljubljana, Slovenia*
[c] *ZAG, Slovenian National Building and Civil Engineering Institute, Dimičeva 12, 1109 Ljubljana, Slovenia*

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Abstract

The influence of different ratios of individual components (silicone surfactant, hydrophilic and lipophilic phase) on the viscoelastic behaviour of semisolid lipophilic emulsion systems was studied. The creams were prepared according to a preliminary experimental design (mixture design). The content of all three phases was varied: surfactant (1–5%), purified water (from 40 to 90%) and white petrolatum (5–59%). Oscillatory rheometry was used as the most appropriate experimental method for the evaluation of the emulsions. The rheological properties were influenced by the ratio of the components. For highly concentrated systems the predominant elastic response in the whole frequency range was measured. The cross-over point is characteristic for the concentrated systems. For the low concentrated systems, viscous behaviour is predominant. Rheometry has also been employed to follow and evaluate physical stability as one of the critical factors of emulsion systems. The dynamic rheological parameter, tan δ, has been chosen as the basis for developing mathematical models (linear, polynomial, neural) to forecast stability related to the content of the separate components in emulsion systems. After testing the linear models their non agreement to statistical criteria for a good model F_{reg}, F_{lof}, CC, DC, and RMS was found. The two-level neural network has been proven to be a statistically acceptable model, as were the polynomials of the second order. The two-level neural network model was also evaluated and the results have shown a great degree of reliability. The prediction of tan δ using a neural network model was found to be of great interest for the contemporary pharmaceutical formulation design because a lot of additional testing can be omitted.

Keywords: Silicone surfactant; Oscillatory rheometry; Viscoelasticity; Semisolid emulsions; Physical stability; Models; Polynomials; Neural networks

* Corresponding author.

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1. Introduction

Semisolid emulsion systems are complex polydispersed gels in which surfactants interact with themselves and with lipophilic or hydrophilic phase (Eccleston, 1986). In the past years semisolid lipophilic emulsion systems did not represent an interesting research field as they had limited therapeutic applications. But today these systems are gaining importance because of their many advantages. They represent physically, chemically and microbiologically stable systems without added preservatives. The area is expanded mostly because of new, very effective surfactants which enable the incorporation of large amounts of water and thus the production of so-called 'light' creams.

Silicone surfactants are representatives of these new surfactants. They are among the most widely used compounds in the formulation of skin care products, because of their physiological acceptance, thermal and chemical stability, and excellent physical characteristics like smoothness and nongreasiness after application (Starch, 1990; Müller-Goymann, 1992; Chandra et al., 1994). Their use in pharmaceutical formulations is still infrequent.

Successful planning and formulation of pharmaceutical emulsion systems demands good knowledge of mechanisms which cause processes of physical instability, such as flocculation (aggregation), sedimentation, flotation and coalescence (Friberg et al., 1996). Problems of physical stability were perhaps one of the main reasons why these systems have not been used to their best advantage. For observation and evaluation of extent of instability there is still no quick and reliable method to be useful for both liquid and semisolid o/w or w/o emulsion systems, sensitive enough to detect indications of instability before they become visible. There are many different procedures and methods to follow changes under normal and stress conditions: rheometry, droplet-size analysis, dielectric measurements, microscopy, DSC (Folgar and Müller-Goyman, 1994; Rieger, 1991). The schemes for stability testing of semisolid emulsion systems are not absolute: by testing a new sample, a plan has to be created for each formulation separately, with respect to its composition. Many comparisons with similar systems whose stability is known and tested (an internal standard), is necessary. While rheometry is one of the important methods for elucidation of the structure of semisolid systems, changes in rheological behaviour can signify instability or at least indicate a particular kind of instability. Therefore, rheological measurements need to be carefully planned and performed (Zografi, 1982).

Simulation is the modern iterative method which can imitate the function (operation, activity) of some real processes. The results of the simulation give additional knowledge of the investigated system. The simulation tools in our investigation were the neural network and the polynomial models. The most important advantage for using neural network models is that they can be used also for non-linear relations between factors and responses. The simulation of the system effects is usually very good (good results of testing of models even outside the limits of the factors). The trained neural network model is simple to use, and close study of the results of the neural network gives us (for inspection of different contours and simulated values) much consequential and useful information about the studied system.

The purpose of the present paper was to explain the influence of different ratios of individual components (silicone surfactant, hydrophilic and

Table 1
The composition of semisolid lipophilic emulsion system according to the constrained mixture design

Sample	Surfactant	Purified water	White petrolatum
I	0.03	0.67	0.30
II	0.05	0.90	0.05
III	0.01	0.90	0.09
IV	0.01	0.40	0.59
V	0.05	0.40	0.55
VI	0.01	0.65	0.34
VII	0.05	0.65	0.30
VIII	0.03	0.90	0.07
IX	0.03	0.40	0.57

Table 2
The input data, values of tan δ, for modelling

Sample	y_1	y_2	y_3	y_4	y_5	y_6	y_7	y_8	y_9
1a	0.7780	0.9215	0.9591	0.8372	0.8819	0.9334	0.8799	1.084	0.9025
1b	0.8409	0.8391	0.8777	0.9141	0.8797	0.8915	0.9725	0.8755	0.9529
1c	0.8892	0.7790	0.8318	0.9815	0.8719	*0.5214*	0.9745	0.917	0.9823
1d	0.8831	0.7642	0.8451	0.8177	0.8297	1.358	0.9355	0.8911	1.023
1e	0.7954	0.7871	0.7793	0.8180	0.8589	1.408	1.047	0.9687	0.8812
1f	0.9347	0.6951	0.8805	0.9573	0.8806	0.9197	0.9471	0.969	0.9318
2	0.4515	0.5037	0.3325	0.3156	0.3106	0.2908	0.2862	0.3143	0.2855
3	0.3887	0.4445	0.2772	0.3071	0.3155	0.3095	0.3234	0.3323	0.3481
4	2.5790	2.7540	3.8470	3.9140	3.379	4.112	4.274	4.645	3.482
5a	2.0730	1.6390	2.7790	2.6230	2.212	2.925	3.002	3.345	3.503
5b	2.1440	1.9160	2.2950	2.3290	2.753	2.497	3.015	3.037	4.035
6	0.9180	0.9661	0.9229	0.9737	1.044	1.072	0.9889	1.042	0.9601
7	0.8187	0.7408	0.7151	0.8228	0.7518	0.8826	0.8959	0.9134	1.029
8	0.5003	0.2932	0.3152	0.3141	0.3071	0.3465	0.3175	0.3088	0.3224
9	2.2680	2.6630	2.7440	2.4580	4.461	3.622	3.631	3.688	3.162

lipophilic phase) in emulsion systems on the structure, which is reflected in their rheological behaviour and has a consequence also in their physical stability. The results of rheometric measurements (dynamic rheological parameter tan δ) were chosen as the basis for the development of mathematical models (linear, polynomials, neural) to forecast stability, depending on the content of separate components in the tested emulsion systems.

2. Materials and methods

2.1. Materials

The silicone surfactant used is a mixture of polysiloxane–polyalkylene–polyether copolymer and non-ionic surfactants (ABIL WE 09®, Th. Goldschmidt, Essen, Germany). White petrolatum and purified water meet the requirements of DAB 10.

2.2. Preparation of w/o semisolid emulsion systems

The tested lipophilic semisolid emulsion systems containing silicone surfactant were prepared by own prescription according to a preliminary experimental design. The constrained mixture design was chosen, where the sum of all three components was equal to 100%. The content of components was varied: silicone surfactant (1–5%), white petrolatum as the lipophilic phase (5–59%), and purified water as the hydrophilic phase (40–90%) (Table 1). Low energy emulsification was selected a method of preparation.

2.2.1. Procedure

The silicone surfactant and white petrolatum were stirred at ambient temperature. Thereafter the purified water was added in small portions while mixing. The creams were finally mixed for 3 min using a high-speed mixer (Ultra Turrax T 25, Janke & Kunkel, Ika Labortechnik, Staufen, Germany) at 8000 rpm.

2.3. Rheology

A rotational and oscillatory viscometer (Rheolab MC 100, Paar-Physica, Stuttgart, Germany) was used. All experiments were performed with a KP 22 cone and plate measuring system (diameter = 25 mm, $\alpha = 1°$, cone–plate distance = 50 μm) at a constant temperature (20 ± 0.2°C).

In dynamic mechanical spectroscopy the stress response of a viscoelastic material subjected to a sinusoidal varying strain is monitored as a func-

tion of strain amplitude or frequency. The viscoelastic properties are expressed with the following dynamic parameters: (1) storage modulus (G', Pa), characterizing the elastic behaviour and representing a quantity of energy reversibly stored in the system; (2) loss modulus (G'', Pa), characterizing the viscous (plastic) behaviour, representing a quantity of irreversibly lost energy; (3) loss factor, $\tan\delta = G''/G'$, indicating the ratio between the viscous and elastic portion of the sample and hence also the ratio between the amount of dissipated and stored energy.

In order to determine the linear viscoelastic area the experiments were carried out at constant frequency (1 Hz) in an amplitude range from 0.05 to 10 (deformation sweep). Once this region was established, the frequency sweep was performed at an amplitude within the linear region (0.2) and the

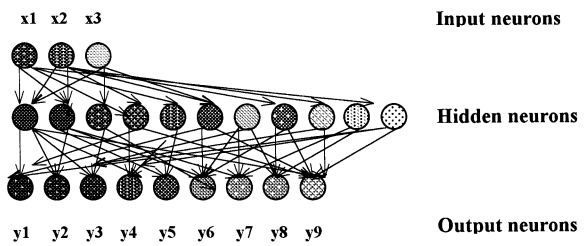

Fig. 1. Architecture of the used back-propagation neural network.

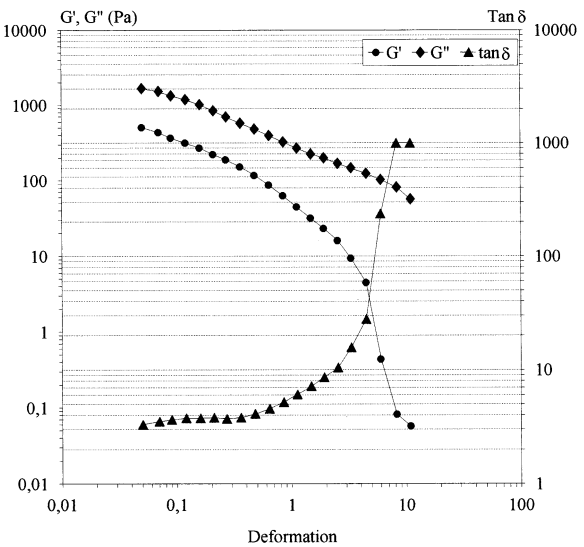

Fig. 2. Determination of linear viscoelastic area for the low concentrated emulsion system (sample V); $v = 1$ Hz.

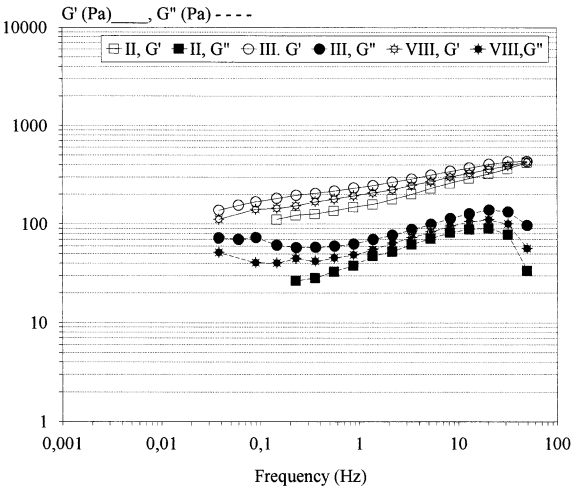

Fig. 3. High concentrated semisolid emulsions: G' and G'' dependent on frequency ($\delta = 0.2$, after 1 month storage).

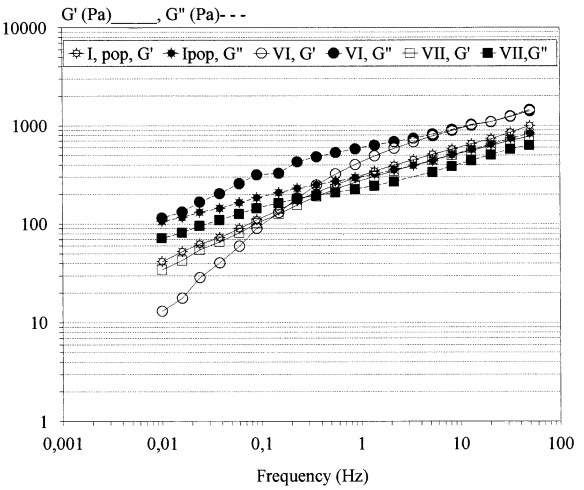

Fig. 4. Concentrated semisolid emulsions: G' and G'' dependent on frequency ($\delta = 0.2$, after 1 month storage).

frequency range from 0.01 to 50 Hz. All rheological parameters were calculated using Physica Software.

The physical stability during ageing was followed for 12 weeks. After preparation, rheological measurements were performed following the following ageing plan; at 1, 2, 3, 4, 6, 8, 10 and 12 weeks. As a measure of evaluation of physical stability, the changes of dynamic parameter tan δ were selected.

2.4. Modelling

The input data for the neural network and polynomial models were the results of oscillation measurements. The absolute value of tan δ at frequency 5.32 Hz was used (Table 2). The first experiment was replicated six times as the measurement error was limiting when the neural network model stopped training (because of over-training problems). At this point the RMS (root mean square of the difference between experimental and simulated tan δ values) was the same as the RMS_m (root mean square of the difference between the particular experimental value and mean experimental value). The correlation between selected factors and tan δ were studied with the models according to the ageing plan. Selected factors were the contents of particular emulsion components: silicone surfactant, x_1; purified water, x_2; and white petrolatum, x_3. The responses represented values of tan δ at different times: y_1, after the preparation; y_2, after 1 week; y_3, after 2 weeks; y_4, after 3 weeks; y_5, after 4 weeks; y_6, after 6 weeks; y_7, after 8 weeks; y_8, after 10 weeks; y_9, after 12 weeks.

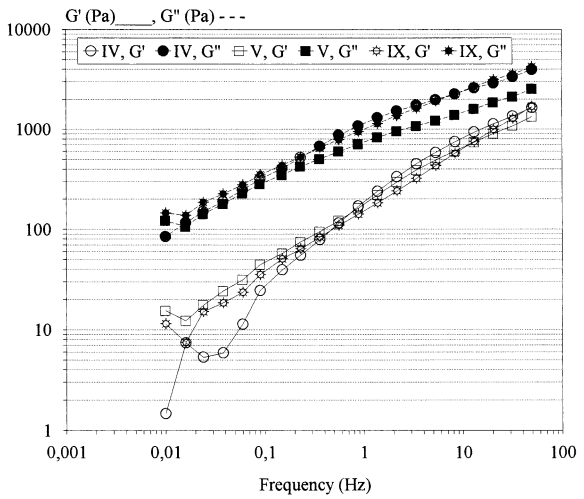

Fig. 5. Low concentrated semisolid emulsions: G' and G'' dependent on frequency ($\delta = 0.2$, after 1 month storage).

Table 3
Mean values, S.D. and R.S.D. of tan δ for a particular tested system during a period of 3 months ($\upsilon = 5.32$ Hz)

Sample	Tan $\delta \pm$ S.D.	R.S.D.
I	0.908 ± 0.091	9.98
II	0.343 ± 0.079	22.93
III	0.338 ± 0.050	14.86
IV	3.665 ± 0.685	18.68
V	2.667 ± 0.585	21.94
VI	0.988 ± 0.054	5.51
VII	0.841 ± 0.100	11.89
VIII	0.336 ± 0.063	18.80
IX	3.189 ± 0.717	22.48

S.D., standard deviation; R.S.D., relative standard deviation, expressed in %.

2.4.1. Linear models

The linear polynomial models were as follows:

$$Y_j = A*x_1 + B*x_2 + C*x_3 \quad (1)$$

These are typical linear models for the mixtures in which the sum of all factor values is equal to 1 or 100%, introduced by Scheffe (Wadsworth, 1990). The significance of the factor according to the examined response can be seen from the size of the parameter of the particular factor in the linear model. The inverse proportion or proportion correlation between factor and response can be determined from the sign of the parameter.

2.4.2. Quadratic models

Quadratic polynomial models were as follows:

$$Y_j = A*x_1 + B*x_2 + C*x_3 + D*x_1*x_2 + E*x_1*x_3 + F*x_2*x_3 \quad (2)$$

The procedure for the determination of incomplete quadratic models involved:

First step: determination of linear model.

Second step: determination of all possible models with different combinations of terms of quadratic polynomial and one term of the cubic polynomial. For example, there were 15 possible combinations of terms:

$$y_1 = a_{1a}*x_{1a} + {}_{1b}*x_2 + a_{1c}*x_3 + a_{1d}*x_1*x_2$$

$$y_2 = a_{2a}*x_1 + a_{2b}*x_2 + a_{2c}*x_3 + a_{2d}*x_1*x_3$$

$$y_3 = a_{3a}*x_1 + a_{3b}*x_2 + a_{3c}*x_3 + a_{3d}*x_2*x_3$$

$$y_4 = a_{4a}*x_1 + a_{4b}*x_2 + a_{4c}*x_3 + a_{4d}*x_1*x_2*x_3$$

Table 4
Statistical evaluation of the linear polynomial models $Y_j = A^*x_1 + B^*x_2 + C^*x_3$

Responses	F_{reg}	F_{lof}	CC	DC	RMS (%)	RMS_m(%)
y_1	36.8594	48.4553	0.8245	0.8496	11.8693	2.3111
y_2	24.5543	24.7843	0.8356	0.8591	13.8439	3.7332
y_3	26.1689	21.5830	0.7832	0.8142	12.6375	3.6414
y_4	25.9299	40.0002	0.7779	0.8096	12.1156	2.5909
y_5	19.2630	36.2590	0.7929	0.8225	14.6156	3.2787
y_6	27.1471	5.1898	0.8196	0.8454	13.4252	7.3890
y_7	29.8802	260.3536	0.8181	0.8441	12.9052	1.0931
y_8	26.5652	64.9652	0.7958	0.8249	13.3502	2.2508
y_9	30.4633	21.9393	0.7232	0.7628	12.989	3.7135

Table 5
Statistical evaluation of the incomplete quadratic polynomial models $Y_j = A^*x_1 + B^*x_2 + C^*x_3 + D^*x_1^*x_2 + E^*x_1^*x_3 + F^*x_2^*x_3$

Responses	F_{reg}	F_{lof}	CC	DC	RMS (%)	RMS_m (%)
y_1	359.572	1.587	0.997	0.998	2.260	2.311
y_2	86.159	3.902	0.985	0.990	5.174	3.733
y_3	102.538	2.907	0.9946	0.9961	4.558	3.641
y_4	64.134	10.859	0.952	0.966	5.431	2.591
y_5	35.194	17.481	0.966	0.973	9.447	3.279
y_6	62.759	0.494	0.99	0.993	6.221	7.389
y_7	1043.521	3.377	0.9832	0.989	1.309	1.093
y_8	253.980	3.784	0.985	0.989	3.085	2.251
y_9.	168.776	1.789	0.957	0.970	4.016	3.714

$F_{regkrit} = 3.482$; $F_{lofkrit} = 4.757$.

$$y_5 = a_{5a}*x_1 + a_{5b}*x_2 + a_{5c}*x_3 + a_{5d}*x_1*x_2 + a_{5e}*x_1*x_3$$

$$y_6 = a_{6a}*x_1 + a_{6b}*x_2 + a_{6c}*x_3 + a_{6d}*x_1*x_3 + a_{6e}*x_2*x_3$$

$$y_7 = a_{7a}*x_1 + a_{7b}*x_2 + a_{7c}*x_3 + a_{7d}*x_1*x_2 + a_{7e}*x_2*x_3$$

$$y_8 = a_{8a}*x_1 + a_{8b}*x_2 + a_{8c}*x_3 + a_{8d}*x_1*x_2 + a_{8e}*x_1*x_2*x_3$$

$$y_9 = a_{9a}*x_1 + a_{9b}*x_2 + a_{9c}*x_3 + a_{9d}*x_1*x_3 + a_{9e}*x_1*x_2*x_3$$

$$y_{10} = a_{10a}*x_1 + a_{10b}*x_2 + a_{10c}*x_3 + a_{10d}*x_2*x_3 + a_{10}e*x_1*x_2*x_3$$

$$y_{11} = a_{11a}*x_1 + a_{11b}*x_2 + a_{11c}*x_3 + a_{11d}*x_1*x_2 + a_{11e}*x_1*x_3 + a_{11f}*x_2*x_3$$

$$y_{12} = a_{12a}*x_1 + a_{12b}*x_2 + a_{12c}*x_3 + a12d*x_1*x_3 + a_{12e}*x_2*x_3 + a_{12f}*x_1*x_2*x3$$

$$y_{13} = a_{13a}*x_1 + a_{13b}*x_2 + a_{13c}*x_3 + a_{13d}*x_1*x_2 + a_{13e}*x_2*x_3 + a_{13f}*x_1*x_2*x3$$

$$y_{14} = a_{14a}*x_1 + a_{14b}*x_2 + a_{14c}*x_3 + a_{14d}*x_1*x_2 + a_{14e}*x_1*x_3 + a_{14f}*x_1*x_2*x3$$

$$y_{15} = a_{15a}*x_1 + a_{15b}*x_2 + a_{15c}*x_3 + a_{15d}*x_1*x_2 + a_{15e}*x_1*x_3 + a_{15f}*x_2*x_3 + a_{15g}*x_1*x_2*x_3$$

The index of responses: y_l where l (1–15) represents the sequential number of possible combinations of parameters. The index of parameters: a_{lk}, where l represents the same as the former and k (a–g) represents the sequential number of a parameter in a particular model.

Third step: the program automatically determines the best model on the basis of the statistical

Table 6
Size of the parameters of incomplete quadratic polynomial models $Y_j = A^*x_1 + B^*x_2 + C^*x_3 + D^*x_1^*x_2 + E^*x_1^*x_3 + F^*x_2^*x_3$

Parameter	x_1	x_2	x_3	x_1x_2	x_1x_3	x_2x_3	$x_1x_2x_3$
y_1	−62.308	0.363	7.283	69.838	51.100	−7.927	—
y_2	−34.757	0.283	8.425	43.051	—	−8.734	—
y_3	−44.984	0.188	11.576	55.342	—	−12.923	—
y_4	8.665	0.119	10.971	—	−62.618	−11.224	—
y_5	−7.906	0.763	12.151	—	—	−15.554	—
y_6	45.550	0.198	12.784	55.163	—	−13.952	—
y_7	−119.518	0.688	16.031	118.463	—	−22.356	220.566
y_8	−45.407	0.286	14.602	54.733	—	−17.067	—
y_9	24.432	0.641	10.626	−31.506	—	−14.026	—

Table 7
RMS values (%) of tested models

Responses	Two-layer neural network	Incomplete quadratic model	Measurements
y_1	2.293	2.260	2.311
y_2	4.260	5.174	3.733
y_3	4.197	4.558	3.641
y_4	5.336	5.431	2.591
y_5	8.125	9.447	3.279
y_6	5.659	6.221	7.389
y_7	1.723	1.309	1.093
y_8	2.370	3.085	2.251
y_9	5.479	4.016	5.976

analysis (values of F_{lof}, F_{reg}, CC, DC, RMS, RMS_m). F_{lof} is Fisher's ratio or lack-of-fit, CC the correlation coefficient, DC the deterministic coefficient, RMS the root mean square of the difference between simulated and experimental values, and RMS_m the root mean square of the difference between a particular experimental value and the mean experimental value (Deming et al., 1987).

2.4.3. Neural network model

A back-propagation supervised learning algorithm was used for modelling the neural network (Tušar et al., 1992). The supervised learning algorithm deals with known pairs, in our case input (factors)–output (responses). The training procedure is based on the steepest descent type of non-linear regression. The squashing function is sigmoidal. The architecture of the neural network can be seen in Fig. 1. There were three input, 12 hidden and nine output neurones. In Fig. 1 only some connections between neurones are drawn. The input neurones were the contents of the particular emulsion components (surfactant, water, white petrolatum) and the output neurones were the measured values of $\tan\delta$ at different time intervals. The learning term was 0.5 (possible range of values, 0–2) and the momentum term 0.9 (possible range of values, 0–1) (Bajsič et al., 1995).

3. Results and discussion

Lipophilic semisolid emulsion systems containing silicone surfactant were prepared by our own prescription according to a mixture experimental design. The share of all three components: silicone surfactant, purified water and white petrolatum was varied. The resulting emulsions can be divided into three main groups: (1) high concentrated, 90% (w/w) of water phase (samples II, III, VIII); (2) concentrated, approximately 65% (w/w)

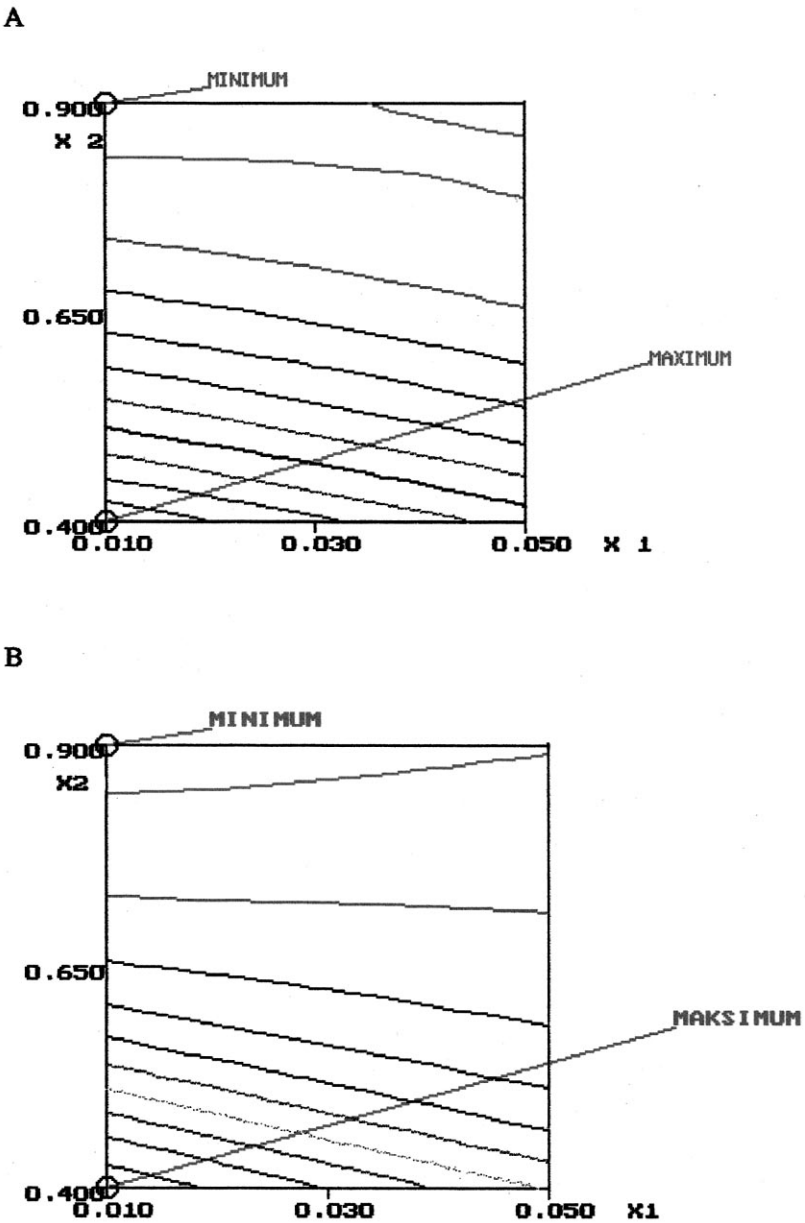

Fig. 6. Comparison on the basis of a graphical presentation of tan δ values dependent on silicone surfactant (x_1) and purified water (x_2) content after 6 weeks calculated with: (A) an incomplete quadratic model; and (B) a two-layer neural network.

of water (samples I, VI, VII); (3) low concentrated, approximately 40% (w/w) of water (samples IV, V, IX).

The microphotographs of emulsions showed a gel network composed of white petrolatum, in which water droplets were dispersed. The size and polydispersity of emulsified droplets depended on the water phase content (Gašperlin et al., 1994).

Table 8
Simulated (tan δ-S) and experimental values of tan δ (tan δ-M) for two new emulsion samples, not included in the experimental design

	x_1	x_2	x_3	Tan δ-M	Tan δ-S
Sample 1	0.05	0.50	0.45	1.45	1.38
Sample 2	0.05	0.70	0.25	0.73	0.66

3.1. Viscoelastic behaviour

The linear viscoelastic range of investigated systems (an example is given in Fig. 2), was evidently observed by deformations smaller than 1.0, according to the constant values of tan δ. In this region the values of storage modulus (G') stay nearly constant, but with the increasing deformations they fell quickly. Such behaviour is attributed to the effect of strain amplitude on the structure of emulsions; at higher deformations some changes of droplet arrangement may occur (Tadros, 1994). The loss modulus values (G'') for the particular sample stayed nearly constant at the chosen amplitude range.

Once the linear viscoelastic area was established, experiments were performed as a function of frequency. Elastic behaviour was predominant for high concentrated systems in the whole frequency range. The incorporation of such an amount of water (as inner phase) was possible because of polydispersity: empty places between larger droplets were filled with smaller ones. Because of the small distance between the droplets, the chains of adsorbed polymeric surfactant molecules at the droplet surface are forced to interpenetrate. This forced interpenetrating is responsible for the dominant elastic response (Fig. 3).

The second group, concentrated emulsion systems, exhibited the cross-over point. At lower frequencies, loss modulus was higher than storage modulus; the system exhibited a more viscous than elastic response. In this area the energy dissipation is relatively larger in comparison to the elastic energy stored in the system. At frequencies higher than the cross-over point, this energy dissipation is insignificant and the system stores most of the energy; the elastic response prevails at the same phase ratio (Fig. 4).

For the low concentrated systems viscous characteristics prevailed in the whole frequency range. The ratio between the hydrophilic and the lipophilic phase, respectively, a smaller volume fraction of inner water phase was found as a decisive factor influencing the prevailing viscous behaviour. The emulsified droplets could be situated relatively far away from each other and steric interactions among them were infrequent (Fig. 5). The viscoelastic characteristics of the prepared lipophilic semisolid emulsion systems containing silicone surfactant were influenced mostly by the hydrophilic/lipophilic phase ratio, while the con-

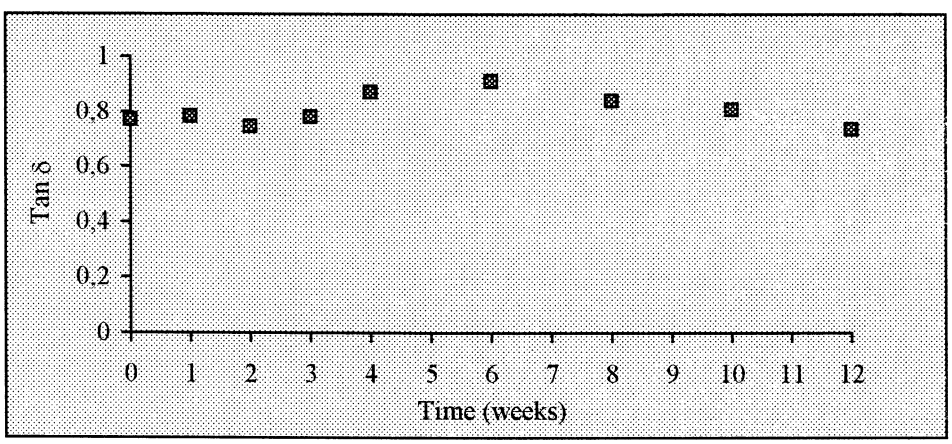

Fig. 7. Predicted values of tan δ during ageing calculated with a neural network for a selected formulation ($\nu = 5.32$ Hz).

centration of the surfactant phase played no major role.

3.2. Evaluation of physical stability

For the evaluation of physical stability of emulsions dynamic parameter tan δ was used. Values tan $\delta < 1$ characterize predominant elastic behaviour, while values tan $\delta > 1$ indicate prevailing viscous behaviour. The changes of tan δ during ageing are shown in Table 2. We have established that all prepared emulsions were physically stable during a period of 1 year. No visual signs of physical instability were observed. All systems also stayed microbiologically stable, although no preservatives were added. The size of emulsified droplets was too small to allow the growth of micro-organisms.

As a criterion for classification, statistical parameter R.S.D. (relative standard deviation) was employed. It represents the deviation in % of mean value of tan δ for a particular sample during a period of 3 months (Table 3). The smallest R.S.D. was exhibited by concentrated emulsion systems (I, VI and VII), followed by low concentrated systems (IV, V and IX) and high concentrated ones (II, III and VIII). The latter were found to be unsuitable for pharmaceutical use because of their prevailing elastic behaviour.

The results enable the statement that, for the preparation of physically stable emulsion systems, 1% (w/w) concentration of silicone surfactant is sufficient. The surfactant used is a polymeric compound composed of the hydrophilic polyether group oriented into the inner water phase and lipophilic polyalkyl groups oriented into the white petrolatum. The polysiloxane backbone, being hydrophobic and lipophobic, strengthens the whole molecule at the interface. The silicone surfactant substantially contributes to the distinct physical stability of emulsion systems, following the mechanisms of reducing interfacial tension and steric stabilization.

3.3. Modelling

From the statistical analysis of the linear polynomial models according to F_{reg}, F_{lof}, CC, DC and RMS, it can be seen that the models do not represent the system very well (high values of F_{lof} and also higher values of RMS in comparison with RMS_m) (Table 4). Consequently, the higher-order polynomials must be used.

A statistical analysis of the second-order polynomial models showed that the incomplete quadratic polynomials represented the studied system very well (Table 5). The term $a^*_{lk}x^*_2x_3$ performed the interaction between water and white petrolatum on the one hand and tan δ, on the other. It appeared in all models (for all nine tan δ) and it was inversely proportional to tan δ (Table 6). Terms $a^*_{lk}x_2$ and $a^*_{lk}x_3$ showed a constant relationship, proportional to tan δ during ageing. A completely different situation was found for $a^*_{lk}x_1$, representing the silicon surfactant: it was found to be proportional (for y_4, y_6, y_9) or inversely proportional (for y_1, y_2, y_3, y_5, y_7, y_8) to tan δ. Almost the same situation occurred for terms which include x_1 ($a^*_{lk}x^*_1x_2$, $a^*_{lk}x^*_1x_3$, $a^*_{lk}x^*_1x^*_2x_3$). These terms showed inverse proportionality or proportionality to tan δ, or they were negligible. We can conclude that the content of the silicone surfactant does not constantly affect tan δ. The findings correlate with the results concerning viscoelastic behaviour.

The comparison between used models (neural network and incomplete quadratic polynomials) was performed statistically and graphically. The results of statistical evaluation based on calculated RMS values of tan δ are shown in Table 7. Furthermore, RMS_m values of experimental tan δ in comparison with the calculated ones showed approximately the same range of values. The size of RMS values calculated on the basis of incomplete quadratic models are close enough to the RMS_m values, so the explanation of correlation between the factors and tan δ can be reliably given. The calculated RMS values with the neural network are even a little bit closer to the RMS_m.

In Fig. 6 the calculated contours based on the neural network and incomplete quadratic model (Table 6, row 6) are shown. The tendency and shape of lines in the contours were found to be practically the same. For any combination of x_1 and x_2 values the content of white petrolatum x_3 is determined as follows:

$$x_3 = 1 - (x_1 + x_2) \quad (3)$$

It can be seen that factor values in maximum and minimum are the same. The calculated values of tan δ in minimum with neural network is 0.254, with a polynomial value of 0.247, whereas the real value is 0.31. In maximum, the calculated value with the neural network is 4.145, with a polynomial value of 3.678, and a real value of 4.11. On the basis of this comparison the neural network model was found to be more accurate.

The neural network was tested with some new experiments (Table 8). These samples were not included in the process of network training. Tan δ of the tested samples revealed that the reliability of the neural network model was high enough for the prediction of the physical stability of semisolid emulsion systems with silicone surfactant.

On the basis of a trained neural network the following actions can be undertaken:

(1) Prediction of tan δ for selected formulation, acceptable for pharmaceutical use. For a certain formulation, tan δ can be predicted during ageing. For example, we would like to know how tan δ changes during ageing for a selected formulation (1% of surfactant, 70% of purified water and 29% of white petrolatum). The results of the neural network model are presented in Fig. 7.

(2) Coincidental search of optimal formulation. Optimal formulations can be calculated with the trained neural network according to our specifications. For example, the content of purified water must be between 80 and 90%, and we would like to achieve a tan δ value of approximately 0.5 after 1 month of storage. In this case the results of modelling are: $x_1 = 0.01$, $x_2 = 0.80$, $x_3 = 0.19$, tan $\delta = 0.480$.

(3) The study of influences of particular factors with the inspection of the calculated counters.

4. Conclusions

Oscillatory rheometry was employed for viscoelastic behaviour and physical stability evaluation of lipophilic semisolid emulsion systems containing silicone surfactant. The oscillation experiments of the high concentrated systems exhibited a predominantly elastic response in the whole frequency range. The cross-over point is characteristic for the concentrated emulsions and for the low concentrated systems the viscous behaviour is predominant. With regard to the results of rheological behaviour of the investigated systems, only the water/white petrolatum ratio was found to be decisive.

Physical stability is one of the most critical parameters of the emulsion systems. All the prepared systems were physically stable during a period of 1 year. Dynamic oscillatory parameter tan δ was chosen as the basis for the development of mathematical models to forecast the stability depending on the content of the individual component in an emulsion. The polynomials of the second order were found to describe the relation between factors and responses almost the same as the neural network model. The two-level neural network was proven to represent a statistically acceptable model. This model was also evaluated and the results have shown a great degree of reliability. The prediction of tan δ using a neural network model was found to be of great interest for a pharmaceutical formulation design because a lot of additional testing can be omitted.

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